REMARKS

Status of the Specification

The Specification has been amended to correct a mistake in the English translation of the Specification in which the word "aspiration" was mistakenly for "respiration," and Applicants include herewith the statement of translator Sonoko Tsukyama in support.

The Specification has been amended to recite all registered trademarks in capitol letters, as suggested by the Examiner.

No new matter has been added.

Status of the Claims

Claim 6 has been canceled; claims 7-18 are withdrawn; claims 1-5 are currently amended; and claims 19-28 have been added.

Claims 1-5 have been amended to more clearly describe the presently claimed invention. Support for the current amendments to claims 1-5 is found in the originally filed claims and by the Specification as follows:

- Support for the amendment to claim 1 reciting, "a protein involved in proliferation or differentiation of cells or regulating cell cycles of a mammalian cell," is found on page 13, lines 15-17 of the Specification.

- Claim 1 has been amended to recite the limitations of canceled claim 6, support for which is found in the original claims.

- Support for the "growth rate" amendments to claims 1, 2 and 5 is found on page 12, line 14 to page 13, line 5 of the Specification.

- Claims 1-5 have been amended to improve grammar.

New claims 19-28 have been added. Support for these claims is found in the original claims and in the Specification as follows:

- Support for the claim 19 limitation reciting a recombinant expression vector that encodes a heterogeneous protein is found in the paragraph bridging pages 20-21 of the Specification.

- Support for the claim 19 limitation reciting that the expression of the heterogeneous protein causes changes in growth state can be found on the paragraph bridging pages 28-29 of the Specification.

- Support for the claim 19 limitation which specifies the heterologous protein expressed by the yeast strains of the invention controls proliferation of mammalian cells or regulates the cell cycle of mammalian cells is found on page 13, lines 15-17 of the Specification.

- Support for the claim 19 limitation which recites that the growth state of the transformed yeast of the invention is sensitized because of respiration ability deficiency is found in the paragraph bridging pages 11 – 12 of the Specification.

- Support for the claim 19 step of comparing the growth states of the test and control cultures is found in the paragraph bridging pages 28 and 29 of the Specification.

- Support for new claims 19-26 is found in the originally filed claims and in the Specification at page 14, line 17 to page 16, line 12.

- Support for new claims 27-28 is found in the originally filed claims and in the Specification at page 16, line 13-23.

No new matter has been added.

Status of the Information Disclosure Statements of March 3, 2005 and July 15, 2005

The Examiner has indicated that the Information Disclosure Statements (IDS) submitted by Applicants on March 3 and July 15, 2005 fail to comply with 37 CFR 1.98(a)(2) and 1.98(a)(3), respectively. As a result, the Examiner has entered these IDSs into the file, but has not considered the documents cited therein. (Office Action, page 3). Applicants submit herewith a legible copy of each document of the IDS of March 3, 2005. Also submitted herewith are concise explanations of the relevance of each non-English language document of the IDS filed on July 15, 2005 in the form of English language translations of the Abstracts of each Japanese patent submitted in the July 15, 2007 IDS.

1. Claim Rejections under 35 USC Section 112, First Paragraph – Written Description

The Examiner has rejected claims 1-6 as allegedly failing to satisfy the written description requirement. In support of this rejection, the Examiner states that the Specification only defines heterogeneous proteins as proteins capable of inducing a change in the growing state of a yeast and as protein fragments that have the function of a heterogeneous protein. The Examiner asserts that the genus of claimed heterogeneous proteins is vast and encompasses proteins that are unrelated by structure such as kinases, phosphatases, helicases, DNAses, transcriptases and proteases. The Examiner then finds that Specification's disclosure fails to adequately define the common structural attributes of the claimed genus because the Specification does not provide

relevant identifying characteristics, including a known disclosed correlation between structure and function. (Office Action, pages 4-6). Applicants respectfully traverse.

As a preliminary matter, Applicants point out that claim 6 has been canceled and claims 1-5 have been amended so that they do not recite the "heterogeneous protein" limitation.

New claim 19, however, does recite the "heterogeneous protein" limitation. Here, Applicants point out that a patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). With these points in mind, Applicants direct the Examiner's attention to the fact that the claims specify that the heterogeneous proteins control cell proliferation or regulate cell cycle control. Applicants submit that the classes of proteins that control cell proliferation and regulate cell cycle are well known in the biotechnology field.

In support of this position, Applicants note that, of his own initiative and without citing supporting references, the Examiner recites that kinases, phosphatases, helicases, DNAses, transcriptases and proteases control cell proliferation or regulate cell cycle. Applicants agree that these classes of proteins contain members that are known to control cell proliferation and/or regulate cell cycle control. In further support of Applicants' position, Applicants direct the Examiner's attention to the following exemplary and non-exhaustive list of publications in the field of cell proliferation and cell cycle control:

- Sherr, C. Cancer cell cycles. Science 274:1672-1677 (1996).
- M. Pagano and P. Jackson. Wagging the Dogma: Tissue specific Cell Cycle Control in the Mouse Embryo. Cell 118:535-538 (2004).
- Hershko A, Ciechanover A. The ubiquitin system. Annu Rev Biochem 67:425-479 (1998).
- Reed, S. Ratchets and clocks: the cell cycle, ubiquitylation and protein turnover. Nat Rev Mol Cell Biol 4:855-64 (2003).

- D. Guardavaccaro and M. Pagano. Stabilizers and destabilizers controlling cell cycle oscillators. Mol Cell 22:1-4 (2006).
- Cardozo T. and Pagano M. The SCF ubiquitin ligase: insights into a molecular mechanism. Nature Rev Mol Cell Biol 5:739-753 (2004).
- Petroski MD, Deshaies RJ. Function and regulation of cullin-RING ubiquitin ligases. Nat Rev Mol Cell Bio 6:9-20 (2005).
- Bloom, J. and Pagano, M. Deregulated degradation of the cdk inhibitor p27 and malignant transformation. Seminars in Cancer Biology 13:41-47 (2003).
- Pagano, M. and Benmaamar, R. When protein destruction runs amok, malignancy is on the loose. Cancer Cell 4:251-256 (2003).
- Guardavaccaro, D . and Pagano, M. Oncogenic Aberrations of Cullin-Dependent Ubiquitin Ligases. Oncogene 23:2037-49 (2004).
- Yamasaki L. and Pagano M. Cell cycle, proteolysis and cancer. Curr Op in Cell Biol, 16:623-628 (2004).
- Ang X.L. and Harper J.W. SCF-mediated protein degradation and cell cycle control Oncogene 24:2860-2870 (2005).
- Nakayama KI., Nakayama, K. Ubiquitin ligases: cell-cycle control and cancer. Nature Reviews Cancer 6:369-381 (2006).
- Gallego, M. and Virshup, DM. Post-translational modifications regulate the ticking of the circadian clock. Nat Rev Mol Cell Biol 8:139-48 (2007).

Applicants submit that these publications, together with a myriad of other publications not listed by Applicants in the interest of efficiency, demonstrate that the identity of individual proteins which comprise the presently claimed heterogeneous protein genus are known in the art. In addition, Applicants point out that these publications disclose the exact primary amino acid sequences, three dimensional protein crystal structures and co-crystal structures for a substantial number of the members of the presently claimed heterogeneous protein genus.

Moreover, these publications disclose structure-function correlative studies which identify loss-of-function mutants caused by changes in the primary amino acid sequences of proteins that control cell differentiation and regulate cell cycle. These publications also disclose published studies which correlate changes in primary amino acid sequences of loss-of-function mutants to changes in three dimensional crystal structures of those loss-of-function mutants as compared to the three dimensional crystal structures of corresponding wild-type proteins.

In view of the Examiner's own reasoning and the disclosure of the above-cited publications in the field, together with the myriad of other publications in the actively studied field of cell proliferation control and cell cycle regulation not presently listed, Applicants submit that one skilled in the art is aware of a large number of compounds that would be encompassed by the present claim term, "heterogeneous proteins," as well as the primary, secondary, tertiary and quaternary structures responsible for their proteins function in controlling cell proliferation and cell cycle control are known.

It follows that, under *In re Buchner*, it is not necessary for Applicants' Specification to describe all of the possible "heterogeneous proteins" by naming each individual member of the claimed genus and/or illustrating the three-dimensional structure-function mechanisms that underlie the control of cell proliferation or regulation of cell cycle functions of the presently claimed genus because this information is known in the biotechnology field. Furthermore, under *In Re Buchner*, Applicants submit that it is preferred that Applicants' Specification omits this known information.

Applicants also point out that the Specification describes members of the presently claimed heterogeneous cell differentiation control and cell cycle regulator proteins that the Examiner simply ignores in imposing the written description rejection. Namely, the Specification describes Tob and Caf family proteins as members of the presently claimed heterogeneous proteins (see for example page 5 line 12 – page 7, line 10 of the Specification), and documents their reduction to practice in the screening method of the invention, both independently and

simultaneously, in the Examples. Moreover, the exact amino acid sequences of the domains of import to the function of Tob and Caf proteins are set forth in the Sequence Listing and on pages 14-17 of the Specification. Applicants submit that this disclosure provides structure-function correlation, to which the Examiner fails to give proper evidentiary weight by simply not taking it into consideration in imposing the written description rejection.

In view of the above-discussed state of knowledge in the art and the significant structure-function description provided by Applicants' Specification, Applicants submit that the originally filed Specification describes the presently claimed invention in a manner that reasonably conveys to a person of skill in the art that Applicants had possession of the presently claimed invention at the time of filing. Accordingly, the written description requirement is satisfied, and Applicants respectfully request reconsideration and withdrawal of this rejection.

2. Claim Rejections under 35 USC Section 112, Second Paragraph

The Examiner has imposed of series of indefiniteness rejections against claims 1-6 (Office Action page 6-8). Applicants have amended claims 1-5 and canceled claim 6, thereby obviating these rejections.

3. Claim Rejections under 35 USC Section 102(b)

The Examiner has rejected claims:

- 1-5 as allegedly independently anticipated by publication WO 01/20020 (2001) to Bounaga et al. and by Florio et al. (1994);
- 1-5 as allegedly anticipated by Superti-ferga et al. (1996); and
- 1, 2 and 5 as allegedly anticipated by Perkins at al.

The Examiner's reasoning for imposing these rejections is found on pages 8-13 of the Office Action, and is not reproduced here. Applicants have amended claim 1 to incorporate the limitations of claim 6, thereby obviating the anticipation rejections.

4. Claim Rejections under 35 USC Section 103

The Examiner has rejected claims:

- claims 1-6 as allegedly obvious over publication WO 01/20020 (2001) to Bounaga et al. in view of Nakahama et al. (1993);
- claims 1-6 as allegedly obvious over Superti-ferga et al. (1996) in view of Nakahama et al. (1993);
- claims 1-6 as allegedly obvious over Florio et al. (1994) in view of Nakahama et al. (1993); and
- claims 1-6 as allegedly obvious over Perkins et al. (1993) in view of Nakahama et al. (1993).

The Examiner's reasoning for imposing these rejections appears on pages 13-17 of the Office Action, and is not reproduced here. Applicants respectfully traverse.

Applicants have canceled claim 6 and amended claims 1-5. Applicants point out that, with the exception of Nakahama et al. (1993), the prior art references relied on by the Examiner in imposing the obviousness rejections are the same as the those relied on by the Examiner in imposing the anticipation rejections, which fail to teach all aspects of the currently claimed screening method as pointed out by Applicants in traversal of the anticipation rejection. Applicants submit that the Nakahama et al. (1993) reference fails to rescue the deficiencies common to Bounaga et al., Superti-ferga et al., Florio et al. and Perkins et al.; so even the combination of the prior art references of record fail to teach the presently claimed invention. The Examiner has therefore failed to establish a *prima fascie* case of obviousness, and the

obviousness rejections are improper. Accordingly, Applicants respectfully request reconsideration and withdrawal of all of the obviousness rejections.

In addition, Applicants have enclosed the Declaration of Dr. Masao Tokunaga. Dr. Tokunaga is a person of ordinary skill in the art and an inventor of the present application. Dr. Tokunaga provides experimental results in his Declaration which support the non-obviousness of the presently claimed invention. Namely, the Declaration provides clear evidence that the instantly claimed respiration deficient yeast strains have lesser variance in generation time and therefore have tighter growth curves than do wild type yeast strains.

As explained by Dr. Tokunaga in his Declaration, the wild-type yeast strains undergo mutation (deletion of respiration ability) at a certain frequency during culture, so that the wild-type strains are developed into a mixture of the wild-type yeast strains and the respiration ability-deficient yeast strains; therefore there is a marked variance in the of the yeast strains, leading to seemingly non-uniform growth rates of the yeast strains in an expressed state and in a non-expressed state of a heterogeneous protein. Consequently, when the pharmacological efficacy of a physiologically active substance is evaluated using wild-type yeast strains, the level of background noise of the data becomes undesirably large, thereby making it difficult to obtain reliable data. On the other hand, the respiration ability-deficient yeast strains do not undergo mutation during culture, always showing stabilized growth ability, so that the respiration ability-deficient yeast strains always show uniform growth rates. As a result, when the pharmacological efficacy of a physiologically active substance is evaluated using the respiration ability-deficient yeast strains, reliable data hardly containing any background noise can be obtained.

Given the surprisingly improved results discussed above and in greater detail in the Declaration of Dr. Tokunaga, Applicants submit the presently claimed invention is indeed non-obvious. Accordingly, Applicants submit that the obviousness rejections are improper, and respectfully request the Examiner reconsider and withdraw all of the obviousness rejections.

5. Conclusion

In view of the above-presented amendments and remarks, Applicants respectfully request immediate allowance of all pending claims, which define subject matter that meets all statutory patentability requirements.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicants respectfully petition for a two (2) month extension of time for filing a reply in connection with the present application, and the required fee of $450.00 is attached hereto.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact John Burr, Registration No 58,475, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

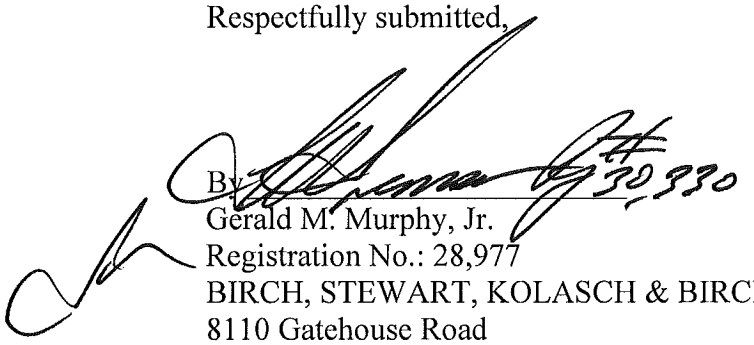
☒ Attached is a Petition for Extension of Time.

☒ Attached hereto is the fee transmittal listing the required fees.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

Dated: May 29, 2007

Respectfully submitted,



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